REMARKS

In the claims

Claim 48 is amended to reinsert the term "effects" which was inadvertently deleted in a previous amendment.

Claims 1, 31 and 48 are amended to clarify claim language by reciting "... using annealing molecular dynamics which incorporates solvation effects."

The preceding amendments are made to clarify the claim language, and are not intended to limit the claims in any way. Further, no new matter is added by the preceding amendments. The Examiner is respectfully requested to enter the preceding amendments.

Accompanying Declaration of William A. Goddard, III under 37 C.F.R. § 1.132

Applicants respectfully request that the Examiner consider and enter the accompanying Declaration of William A. Goddard, III under 37 C.F.R. § 1.132.

Information Disclosure Statement

Applicants respectfully request that the Examiner consider and initial each reference cited in the Information Disclosure Statement submitted herewith.

Indefiniteness rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 stand rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite. Regarding the recitation of "further optimizing...by using annealing molecular dynamics including solvation effects" in claim 1 and corresponding phrases in claims 31 and 48, the Examiner alleges that it is unclear what method/process Applicant is intending to encompass because the claims allegedly do not set forth any steps indicating in what way "annealing molecular dynamics" includes solvation effects. The Examiner requests clarification of the claim language.

According to MPEP § 2173.05(a), "[i]f the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and

if the language is as precise as the subject matter permits, the statute (35 U.S.C. § 112, 2nd Paragraph) demands no more."

As previously noted by Applicants in the reply filed June 25, 2007, the specification exemplifies an annealing molecular dynamics optimization which incorporates solvation effects, for example as recited in part in paragraph [0040]:

> Annealing molecular dynamics was performed on a subset of the energy minimized ligand conformations (*e.g.*, from about 1% to about 20% or more of these configurations) using MPSim software, K.-T. Lim, *et al.* (1997) *J. Comput. Chem.* 18, 501-521, which is incorporated by reference herein, using a full atom force field and solvation effects, such as a continuum description of the solvation using Poisson-Boltzmann method (PBF), D. J. Tannor, *et al.* (1994) *J. Am. Chem. Soc.* 116, 11875-11882, or the surface generalized Born (SGB) model, A. Ghosh, *et al.* (1999) *J. Phys. Chem. B.* 102, 10983-10990, both of which are incorporated by reference herein. Those skilled in the art will recognize that other solvation models can also be used, including, for example, empirical solvation models that estimate solvation free energies as a function of solvent accessible surface area of the protein (such as the Fast Solvation Model (FSM)), as described in R. L. Williams, et al. (1992) Proteins: Structure, Function and Genetics 14, 110-119, which is incorporated by reference herein.

Thus, the specification describes an exemplary annealing molecular dynamics calculation which can employ various force models such as a full atom force field and various models of solvation effects. The specification incorporates by reference scientific literature which describes aspects of a exemplary software package, MPSim, which can be used to perform such calculations. The specification also describes exemplary solvation effect models that can be included in the annealing molecular dynamics calculation, such as a continuum description of the solvation using Poisson-Boltzmann method, the surface generalized Born model, empirical solvation models that estimate solvation free energies as a function of solvent accessible surface area of the protein such as the Fast Solvation Model, and the like.

Consequently, one of skill in the art is reasonably apprised of both the utilization and scope of the invention by reading a phrase in the claims such as "...using annealing molecular dynamics which incorporates solvation effects" in light of the exemplary use of solvation effects in the annealing molecular dynamics example in the specification. The language is as precise as

needed by the subject matter, since one of skill in the art can access publicly available programs such as MPSim, in consultation with the scientific literature incorporated by reference in the specification. Consequently, 35 U.S.C. § 112, 2nd Paragraph demands no more. Nevertheless, in the interest of furthering prosecution, Applicants suggest herein the alternate wording "... using annealing molecular dynamics which incorporates solvation effects." This amendment is made only to address the allegation of indefiniteness, and is not intended to limit the amended claims in any way. Applicants therefore respectfully request that the corresponding rejection be withdrawn.

Should the Examiner continue to have questions on the revised wording, Applicants respectfully point to MPEP § 2173.02, which states "[s]ome latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement." Thus, should the Examiner wish to reiterate the rejection, Applicants respectfully request that the Examiner precisely specify that which is regarded as indefinite and suggest claim language to Applicants which would improve clarity or precision so as to overcome the rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zou *et al.* (*J. Am. Chem. Soc.*, 1999, Vol. 121, p.8033-8043), in view of Bassolino *et al.* (*Protein Science*, 1996, Vol. 5, p.593-603). Also, claims 1, 2, 9, 31, 37, 48, and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vieth *et al.* (*J. Comp. Chem.*, 1998, Vol. 19, No. 14, p.1623-1631), in view of Moyna *et al.* (*Biopolymers*, 1999, Vol. 49, p.403-413). These references are together referred to as the "cited references" or each individually as a "cited reference."

The framework under which obviousness of a patent claim is judged was set forth by the U.S. Supreme Court in Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966), and is as follows. Under § 103:

- the scope and content of the prior art are to be determined;
- differences between the prior art and the claims at issue are to be ascertained; and
- the level of ordinary skill in the pertinent art resolved.

Based upon the answers to these factual enquiries, the obviousness or nonobviousness of the claimed subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might also be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Accordingly, and at a minimum, in order to establish obviousness of a claim, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Furthermore, and in instances where each and every limitation of the claimed invention can be found in a combination of references, an analysis of an apparent reason to combine the known elements in the fashion claimed should be made explicit. KSR Int'l. Co. v. Teleflex Inc., (04-1350, U.S. S.Ct., April 30, 2007).

The cited references do not teach or suggest the hierarchy embodied in the language of the steps, while the surprising and unexpected results overcome any allegation of prima facie obviousness

The claimed invention is not obvious over Zou *et al.* in view of Bassolino *et al.* nor over Vieth *et al.* in view of Moyna *et al.* because these references do not teach or suggest each and every limitation of the claimed invention, including performance of the required steps according to the hierarchy embodied in the language of the steps. Further, the surprising and unexpected results of the claimed invention overcome any allegation of prima facie obviousness over order or number of steps.

The claimed invention is directed to (claim 1) a method of identifying one or more ligand conformations that bind to a protein, the method comprising:

obtaining structural information for the protein and for one or more ligands;

identifying at least one binding region of the protein;

applying a coarse-grained docking algorithm to identify a plurality of binding conformations for the one or more ligands in the binding region;

selecting a set of best conformations by lowest energy from the binding conformations for the one or more ligands;

optimizing the best conformations using molecular mechanics;

further optimizing a subset of the best conformations by using annealing molecular dynamics which incorporates solvation effects;

minimizing a preferred set of conformations from the subset of the best conformations;

calculating a binding energy for each conformation of the preferred set of conformations;

ranking the conformations of the preferred set of conformations based on the calculated binding energies;

selecting for each of the one or more ligands the conformation of the preferred set of conformations having the lowest calculated binding energy; and

outputting a data file comprising a list of selected ligand-protein conformations having the lowest calculated binding energy, and their respective binding energies;

wherein the method is performed by a programmable processor executing a program of instructions.

The Examiner has alleged that each of the steps recited in the claims can be found suggested or disclosed in one or more of the cited references, albeit by piecing together those steps, regardless of any order in which the references teach their performance.

An element of the claimed invention is the hierarchy of the recited steps embodied in the language, which indicates that a result of a prior step is operated on by a subsequent step to create a result of the subsequent step. For example, in claim 1 above, the "applying" step results in "a plurality of binding conformations..." while the immediately subsequent "selecting" step operates on "the binding conformations" to result in "a set of best conformations..." The hierarchical nature of the invention is described and exemplified throughout the specification, e.g., in paragraph [0007]:

> The invention provides a hierarchy of molecular modeling techniques ... These techniques generally employ a hierarchical strategy ranging from coarse grain to fine grain conformational search methods combined with hierarchical levels of accuracy in scoring functions. Various implementations of the invention use hierarchical combinations of coarse-grain docking methods, fine grain molecular dynamics techniques and scoring functions with different levels of accuracy that include solvation effects, to provide computationally-efficient and accurate models for predicting binding site of ligands in proteins and drug design.

The recitation of "comprising," e.g., in claim 1, permits other steps in addition to the recited steps, repetition or repeated iteration of the recited steps, and the like. Nevertheless, the language of the claimed invention requires each and every step as claimed, which includes performance of the required steps according to the hierarchy embodied in the language of the steps as claimed.

The rejections under 35 U.S.C. § 103(a) assert that the term "comprising...does not exclude additional, unrecited elements or method steps" and that "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" but no reasoning or analysis is advanced as to why the alleged equivalent elements of the cited references would be combined in the hierarchy embodied in the language of the steps as claimed. Furthermore, the new and unexpected results of the claimed invention refute the assertion that "any order of performing process steps is prima facie obvious in the absence of new or unexpected results." According to the accompanying declaration under 37 C.F.R. § 1.132 of William A. Goddard, III, an inventor of the subject application, the trade-offs between practicality and accuracy were well-known at the time of filing of the subject application.

Declaration, Section III. Consequently, simply combining steps from the cited references would be expected to lead to a less practical or even intractable calculation. By contrast, exemplary implementations of the subject invention predicted surprisingly accurate binding sites and configurations for a number of proteins and ligands in a practical, tractable manner. Declaration, Section IV.

For example, Section VI, references 7, 8, and 9 show that protein-ligand configurations predicted by the subject invention are surprisingly stable and accurate when validated with extensive molecular dynamics simulations using infinite membrane and solvent effects. Declaration, Sections IV and VI. Further, ligand-protein configurations which were predicted (references 6, 8, and 9) according to the subject invention were employed to design subsequent mutation experiments, which validated the surprising accuracy of the predicted configurations. Declaration, Sections IV and VI.

In particular, the work reported in reference 9 resulted in a new drug for allergic inflammation, which is now in advanced trials. Predicted ligand structures gave details of the relative binding energies for closely related ligands, even for cases differing by only a factor of two in binding constant. For example, the subject invention surprisingly and correctly predicted the best ligand, which was subsequently shown to have a binding constant 1000 times better (0.8 nM versus 800 nM) than the lead compound identified by traditional pharmaceutical methods. No other computational approach has ever correctly predicted protein-ligand structures for a membrane protein in advance of experimental studies to locate the binding region of the protein, let alone resulting in a potentially important new drug. Declaration, Sections IV and VI.

In conclusion, the cited references do not teach or suggest each and every limitation of the claimed invention because they do not include performance of the required steps according to the hierarchy embodied in the language of the steps. Further, any allegation of prima facie obviousness over order or number of steps is overcome because none of the surprising effects of the claimed invention-neither the surprising practicality and accuracy of the predicted protein-ligand configurations, the surprising improvement in drug design over traditional pharmaceutical methods, nor the first correct prediction in advance of protein-ligand structures

for a membrane protein--would be expected in view of the common knowledge in the art, or from the cited references Therefore, for at least the preceding reasons, the claimed invention is nonobvious over Zou *et al.* in view of Bassolino *et al.* and over Vieth *et al.* in view of Moyna *et al.*

One of ordinary skill would not combine the cited references to arrive at the claimed invention

The claimed invention is not obvious over the references cited by the Examiner because one of ordinary skill in the art would not combine the teachings of the cited references to arrive at the claimed invention, nor would one expect that such a combination would lead to the surprising and unexpected results of the invention. As stated in the accompanying declaration, the trade-offs between practicality and accuracy were well-known at the filing date of the subject application. Declaration, Section III. Computational methods for predicting ligand binding sites in proteins, modeling protein-ligand interactions and drug design could be described in two general categories: (1) thorough, but computationally expensive methods that could predict configurations for certain protein-ligand combinations, but were impractical or intractable in application to the large numbers of ligands typically of interest in drug design; and (2) various methods which made significant compromises in thoroughness and accuracy in order to achieve computational practicality and tractability. Declaration, Section III. For example, as noted in the Declaration, Section III, with regard to calculating solvent interactions, Zou *et al.* state:

> Accounting for the effect of solvent on the strength of molecular interactions has been a longstanding problem for molecular calculations in general and for structure-based drug design in particular. (abstract).
>
> The most obvious method to overcome these problems is to treat solvent molecules explicitly in molecular dynamics or Monte Carlo simulations of binding ...However, *these approaches are currently impractical for screening large numbers of molecules.* (emphasis added, p. 8043, last paragraph, through page 8044, line 3).

Consequently, without more, one of ordinary skill in the art would not combine steps from the cited references, let alone to arrive at the claimed invention, because doing so would be expected to increase the computational complexity and expense of any such combination in comparison to

the method of any cited reference alone, and therefore such a combination would be expected to be impractical or even intractable in comparison the method of any cited reference alone. Furthermore, one of ordinary skill in the art would not expect that such a combination would lead to the surprising and unexpected results of the invention. Therefore, for at least the preceding reasons, one of ordinary skill in the art would not combine the teachings of the cited references to arrive at the claimed invention.

The claimed invention is financially successful and meets a long-felt need in pharmaceuticals

The claimed invention is not obvious over Zou *et al.* in view of Bassolino *et al.*, because the claimed invention and its predictions have been financially successful and have addressed a long-felt need in the pharmaceutical industry.

As stated in the accompanying declaration, the pharmaceutically relevant, financially successful applications of the subject application have secured over $2.5M from major pharmaceutical companies to date because the subject invention addresses a long felt need in the pharmaceutical industry for a practical method that can predict new protein-ligand configurations, allowing structure based drug design methods to effectively research important targets such as G-protein coupled receptors. Declaration, Section V. Even though major pharmaceutical companies typically do not want their research directions to be known to the outside world, they fund this commercially relevant work under Applicants' direction because the subject invention is successful. Declaration, Sections V and VI. In particular, the work reported in reference 9 for Sanofi-Aventis is the first time that theory has led to a new drug for a G-protein coupled receptor, now in advanced trials for allergic inflammation; in fact, no other computational approach has ever correctly predicted protein-ligand structures for a membrane protein in advance of experimental studies to locate the binding region of the protein, let alone resulting in a potentially important new drug. Declaration, Sections V and VI.

Consequently, because the claimed invention and its predictions have been financially successful and have addressed a long-felt need in the pharmaceutical industry the claimed invention is nonobvious thereover.

For at least the preceding reasons, the claimed invention is nonobvious over the respective rejections over Zou *et al.* in view of Bassolino *et al.*, and over Vieth *et al.* in view of Moyna *et al.* Applicants respectfully request that the corresponding rejections be withdrawn.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

Please apply any required charges or credits to deposit account 06-1050.

Respectfully submitted,

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Kraig K. Anderson
Reg. No. 54,961

Customer No. 26181
Fish & Richardson P.C.
Telephone: (650) 839-5070
Facsimile: (650) 839-5071